IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Neil H. Bander
Serial No. : 09/929,546
Filed : August 13, 2001
Title : TREATMENT AND DIAGNOSIS OF PROSTATE CANCER

Art Unit : 1642
Examiner : Gary B. Nickol

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

I, Abbie Celniker, Ph.D., pursuant to 37 C.F.R. § 1.132, declare the following:

1. I am currently employed by Millennium Pharmaceuticals, Inc. as Senior Vice President of R&D Strategy and Operations. I am not an inventor on the above-referenced application. My Curriculum Vitae is attached.

2. I have extensive experience in antibody technology. As can be seen from my Curriculum Vitae, I earned a Ph.D. in Molecular Biology in 1986. My doctoral research concerned immunological studies of human cathespin D. I have been involved in the development of antibody-based projects or products in industry since at least 1986. Since at least 1993 I have held senior research and development positions at Millennium Pharmaceuticals, Genetics Institute, Genetics Institute of Wyeth Ayerst Research, and Genentech Inc. All of these positions included oversight of therapeutic and/or diagnostic antibody projects. My experience extends from years before the priority and filing dates of the above-identified application to the present. During this time, I have worked with and/or supervised numerous individuals of ordinary skill in the art of antibody-based technologies and am well acquainted with the qualifications and abilities of one of ordinary skill in this art. At the time the application was filed, 1996, one of ordinary skill in the art would have understood the structure of antibodies, methods of making them, and at least the basics of how the specific binding properties of antibodies could be useful in therapeutic and diagnostic products. Typically, such an individual would have had a Ph.D. in a biological science and some post-doctoral or industry experience.

3. I have reviewed the specification and the pending claims in the above-referenced application. It is my understanding that the pending claims in the above-referenced application include the following language:

> wherein the antibody or antigen binding portion thereof competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody

As will be described in detail below, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed, would have believed that the specification discloses, and the inventors were in possession of, this subject matter.

4. It is my understanding that this language has been rejected by the Examiner in the above referenced application. The rejection is based on the Examiner's argument that the subject matter set out above was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention.

5. The reader is directed first to page 32, line 28, to page 33, line 2 of the specification of the above-identified application as filed. This passage discusses a particular embodiment wherein antibodies are used to direct two components[1] to a desired site, and provides as follows:

> ***a first biological agent*** is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. The prodrug activator is conjugated with ***a second biological agent according to the invention, preferably*** one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (***emphasis added***).

[1] One component is an inactive drug, or prodrug, and the other is an activator of the prodrug.

From the passage recited above, it is clear to me that the cited text, in combination with the rest of the specification, discloses two types of antibodies[2] --those that compete for binding with an antibody "according to the invention" and those that do not compete for binding with an antibody "according to the invention", the later being preferred in the particular embodiment being described. But whether preferred or not, it is clear from the text that the inventors were in possession of the idea of an antibody which competes for binding with an antibody according to the invention. The text also provides, see, e.g., the last sentence of the quoted passage , what constitutes a competing site and a non-competing site by stating that "whether two biological agents bind to competing or non-competing sites can be determined by conventional competition binding assays." Therefore, the application necessarily discloses the concept of an antibody that competes for binding with an antibody according to the invention. It is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that the specification discloses and the inventors were in possession of this element of the invention, namely, an antibody that competes for binding with an antibody according to the invention.

6. It is also clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that monoclonal antibodies E99, J415, J533 and J591 are "antibodies according to the invention." These four antibodies are disclosed throughout the application as being antibodies of the invention. In fact, the very next sentence, page 33, lines 3-8, after the passage recited above states as follows:

> For example, monoclonal antibodies J591, J533, and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415, on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind.

---

[2] The term "biological agent" is defined at page 16, lines 16-20, to include antibodies. Most of the disclosure in the specification is with regard to antibodies, so one of ordinary skill would undoubtedly view the quoted section as applying to antibodies.

Thus, the application necessarily discloses that monoclonal antibodies E99, J415, J533 and J591 are antibodies according to the invention. Furthermore the specification, in that passage, gives an example of a specific set of antibodies which compete and an antibody that does not compete with members of the group.

7. As indicated in paragraph 5 above, and in particular in the second sentence of the quoted passage, it is clear that the Applicants disclosed a first antibody or portion thereof that competes for binding with a second antibody according to the invention and, as indicated in paragraph 6, monoclonal antibodies E99, J415, J533 and J591 are clearly antibodies according to the invention. It is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed, would have believed that the specification discloses, and the inventors were in possession of, this element of the invention, namely, "antibodies or portions thereof that compete for binding to PSMA with monoclonal antibodies E99, J415, J533 and J591."

8. I want to be clear that I am not saying merely that the text makes it obvious to arrive at "antibodies or portions thereof that compete for binding to PSMA with monoclonal antibodies E99, J415, J533 and J591" or that the specification discloses a general concept of what antibodies might compete and that it is only obvious that these would be E99, J415, J533 and J591. On the contrary, it is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed, would have believed the text itself describes and actually shows possession of the subject matter in question. It is really a rather simple matter: a series of consecutive sentences in the specification build on one another and require this conclusion. I have summarized the situation below, where the relevant text (e.g., page 32, line 28, through page 33line 8) is presented in annotated form:

	Text from the specification		Meaning	
	In a particularly preferred embodiment of the present invention, especially well-suited for killing or ablating normal, benign hyperplastic, and cancerous prostate epithelial cells, a first biological agent is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. (page 32, lines 28-33)			
	The prodrug activator is conjugated with a second biological agent according to the invention, preferably one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (page 32, line 33, to page 33, line 2)		These two sentences tell one of ordinary skill that the applicant was in possession of antibodies which compete with antibodies of the invention and give the meaning of the term compete for binding.	
	For example, monoclonal antibodies J591, J533 and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415, on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind. (page 33, lines 3-8)		This sentence, the next sentence in the specification, tells one that the specific antibodies mentioned in the claim (J415, J591, J533 and E99) are antibodies of the invention.	

Thus, one reading this passage, learns from the first four sentences that antibodies which compete for binding with antibodies of the invention are described. A few lines later one learns that J415, J591, J533 and E99 are antibodies of the invention. It is simply inescapable that the specific examples of antibodies of the invention, J415, J591, J533 and E99, provided in the text can be placed in the context of the earlier sentence. It is to me that, upon reviewing the specification of the above-referenced application, one of

ordinary skill in the art at the time the application was filed, would have believed that the specification discloses, and the inventors were in possession of, antibodies that compete for binding with the listed antibodies, in other words, antibodies that compete for binding with one or more of J415, J591, J533 or E99.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 7/22/04

Abbie Celniker, Ph.D.

20907001.doc

Abbie C. Celniker, Ph.D.
560 Chestnut Street
Newton, MA 02468
Home: 617-332-0067 Fax: 617-969-7030
Acelniker@AOL.com

Education:

1986, Ph.D., Molecular Biology, University of Arizona. Immunological Studies of Human Cathepsin D

1980, B.A., Biology, University of California, San Diego

Experience Overview:

- Extensive experience in the area of pharmaceutical development and commercialization including; functional line and matrix area oversight.
- Biopharmacetuical Pipeline and Portfolio Management for both small and large molecules
- Specific scientific expertise in the areas of transplantation biology, co-stimulation, growth and wasting.
- Technical expertise in the areas of; monoclonal antibody discovery, development and characterization, immunoassay and analytical methods development and Preclinical biology.
- Managerial experience including the management of individuals and diverse groups consisting of individuals from the VP to RA level.
- Compliance experience including the organization and maintenance of GLP and GMP compliant laboratories and information management systems.
- Translational biology experience focused on the integration of novel analytical methods into clinical studies and the movement of therapeutic proteins from research into the clinic.

Employment:

August 2001 to Present Senior Vice President, R&D Strategy and Operations, **Millennium Pharmaceuticals**, Cambridge, MA. Responsibilities include:

- Oversight the Project Management, Scientific Development and R&D Planning and Operations areas.
- Co-Chair of the Pipeline Review Committee responsible for operational and strategic oversight of the R&D pipeline, investment prioritization and technical review of programs from late lead optimization through commercialization.

- Member of the Strategic Portfolio Committee, a subcommittee of the Management Team responsible for integration of R&D, Commercial, Business Development opportunities.

- Interface with the R&D subcommittee of the BOD on pipeline and R&D strategy.

June 2000 to August 2001 Vice President, Biotherapeutics, **Millennium Pharmaceuticals**, Cambridge, MA. Responsibilities include:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Protein Sciences (discovery and process development), Biological Assay Development, Mouse Models Development and the Animal Resources Group.

- Participation on the Discovery Scientific Review Committee, Development Scientific Review Committee and Product Team (development portfolio management)

October 1999 to June 2000, Assistant Vice President, Predevelopment – Biopharmaceutical Core Technologies, **Genetics Institute of Wyeth Ayerst Research**, Andover/Cambridge, MA. Responsibilities included:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Research Protein Supply, Proteomics, Bioanalytical Sciences, Pharmacokinetic and Pharmacodynamic Sciences, Laboratory Animal Resources, Preclinical Scientific Communications, Research Operations and the External Research Department.

- Oversight of "predevelopment process" for therapeutic proteins moving from discovery research into development (Lead Candidate through IND).

- Preclinical Project Team Leader for the Anti-B7.1/Anti-B7.2 Program in GvHD and Renal Transplantation

November 1993 to June 1999, Director /Senior Scientist of Bioanalytical Sciences at **Genetics Institute**, Andover, MA. Responsibilities included:

- Oversight of the Antibody Technology Group, Bioanalytical Sciences and the Preclinical Transcriptional Profiling group (Gene Expression Monitoring).

- The establishment and oversight of a GLP compliant immunoassay lab, including laboratory automation (sample tracking, sample manipulation and data transfer), assay validation and facility management.

- Member of the Analytical Coordinating Group (ACG) responsible for the immunoassays used for identity testing, ligand binding analysis and immunoassays for host cell protein impurities to support process and product development.

- Oversight of the assessment and interpretation of anti-product immune responses for Preclinical and clinical studies.

May of 1993 to November 1993, Associate Director/Senior Scientist, Medicinal and Analytical Chemistry, **Genentech Inc.**, South San Francisco, CA. Responsibilities included:

- Oversight of the Bioanalytical Methods Development group, responsible for immunoassay development for research, Preclinical, clinical and product development support

- Preclinical Research Project Team Leader for the IGF-1 Program

June 1986 to May of 1993, Scientist, Medicinal and Analytical Chemistry, **Genentech Inc.**, South San Francisco, CA. Responsibilities included:

- Development of antibodies and immunoassays for the quantitation of human and animal growth hormones in serum and urine and the assessment of the anti-growth hormone antibody response.

- Development of antibodies and immunoassays for the quantitation of human Insulin-like Growth Factor 1 (IGF-1) and IGF-1 binding proteins in serum and urine to support preclinical and clinical pharmcokinetics and pharmacodynamics

- Development of antibodies and immunoassays for the quantitation of gamma interferon, TNF-alpha, HSA, Human Relaxin, Pro-Relaxin, and Relaxin "A" and "B" chains in serum, urine and cell expression systems

- Development of immunoassays for the quantitation of E. coli and CHO derived host cell protein impurities

1984 to 1986, Research Associate, **University of Arizona Cancer Center**, Veteran's Administration Hospital, Tucson, AZ. Responsibilities included:

- Establishment of primary cells lines from prostate tumor and benign prostatic hypertrophy specimens.

- Development of assays to differentiate cytostatic from cytotoxic biological response modifiers.

- Development of immunohistochemical staining methods for the detection of prostate cancer cells in bone marrow.

Publications:

Takai DK, Craighead, N, Saini, A, **Celniker, A.**, Burkly, L.C., Lee, K.P., Chute, J.P., Harlan, D.M. and Kirk, A.D. Costimulatory molecules are active in the human xenoreactive T-cell response but

not in natural killer-mediated cytotoxicity. Transplantation. 2000 Jul 15;70(1):162-7.

Modi, N., Baughman, S., Paasch, B., **Celniker, A.**, and Smith, S. Pharmacokinetics and pharmacodynamics of TP-9201, a GPIIbIIIa antagonist, in rats and dogs. J Cardiovasc Pharmacol. 1995 Jun; 25(6): 888-97.

Boguniewicz, M., Martin, R., Martin, D., Gibson, U., **Celniker, A.**, Williams, M., and Leung, D. The effects of nebulized recombinant interferon-gamma in asthmatic airways. J Allergy Clin Immunol. 1995 Jan;95(1 Pt 1):133-5

Martin, R., Boguniewicz, M., Hensen, J.E., **Celniker, A.**, Williams, M., Giorno, R., and Leung, D.Y. The Safety and Effects of Inhaled Interferon Gamma in Normal Human Airways. Am Rev of Resp Dis 148: 1677-1682, 1993.

Hartman, M.L., Clayton, P.E., Johnson M.L. Perlman, A.J., **Celniker, A.C.**, Alberti, K.G.M.M. and Thorner, M.O. A Low-Dose Euglycemic Infusion of Recombinant Human Insulin-Like Growth Factor I Rapidly Suppresses Fasting-Enhanced Pulsatile Growth Hormone Secretion in Humans. JCI 91: 2453-2462, 1993.

Stewart, D.R., Overstreet, J.W., **Celniker, A.C.**, Hess, D.L., Cragun, J.R., Boyers, S.P. and Lasley, B.L. The Relationship Between HCG and Relaxin Secretion in Normal Pregnancies vs Periimplantation Spontaneous Abortions. Clin Endo 38: 379-385, 1993.

Simon, C.J.Y., Underwood, L.E., **Celniker, A.** and Clemmons, D.R. 1992. Effects of Recombinant Insulin-Like Growth Factor-I (IGF-I) and Growth Hormone on Serum IGF-Binding Proteins in Calorically Restricted Adults. J. Clin Endocrinol. Metab. 75: 603-608, 1992

Lieberman, SA, Bukar, J, Chen, SA, **Celniker, AC**, Compton, PG, Cook, J, Albu, J, Perlman, AJ, and Hoffman, AR. 1992. Effects of Recombinant Human Insulin-Like Growth Factor-I (rhIGF-I) on Total and Free IGF-I Concentrations, IGF Binding Proteins, and Glycemic Response in Humans. J. Clin Endocrinol Metab. 75: 30-36, 1992.

Albini, C.H., Sotos, J., Sherman, B., Johanson, A., **Celniker, A.**, Hopwood, N., Quattrin, T., Mills, B., and MacGillivray, M.H. 1991. Diagnostic Significance of Urinary Growth Hormone Measurements in Children with Growth Failure: correlation between serum and urine GH. Pediatric Research 29: 619-622, 1991.

Ferraiolo, B.L., Winslow, J., Laramee, G., **Celniker, A** and Paul Johnston. The Pharmacokinetics and Metabolism of Human Relaxins in Rhesus Monkeys. Pharmaceutical Research, 8: 1032-1038, 1991.

Girard, J., **Celniker, A.**, Price, A., Tanaka, T., Walker, J., Welling, K., and Albertsson-Wikland, K. Urinary Measurement of Growth Hormone Secretion. Acta Paediatr Scad [Suppl], 366: 149-154, 1990.

Stewart, D.R., **Celniker, A.C.**, Taylor, C.A., Gragun, J.R., Overstreet, J.W. and Lasley. B.L. Relaxin in the Peri-Implantation Period. J. Clin Endocrinol and Met, 70: 1771, 1990

Celniker A.C., Chen, A.B., Wert, R.M. and Sherman, B.M. Variability in the Quantitation of Circulation Growth Hormone Using Commercial Immunoassays. J. Clin Endocrinol and Met, 68: 469, 1989

Ahmann, R.R., Garewal, H.S., Schifman, R., **Celniker, A**. and Rodney, S. Intracellular Adenosine Triphosphate as a Measure of Human Tumor Cell Viability and Drug Modulated Growth. J. In Vitro Cell Dev Biol 23: 474, 1987

Montgomery, D.W., **Celniker, A.** and Zukoski, C.F. Didemnin B--An Immunosupressive Cyclic Peptide that Stimulates Murine Hemagglutinating Antibody Responses and Induces Leukocytosis In Vivo. Transplantation 43: 133, 1987

Nagle, R.B., Ahmann, F.R., McDaniel, K.M., Paquin, M.L., Clark, V.A. and **Celniker, A.** Cytokeratin Characterization of Human Prostatic Carcinoma and Its Derived Cell Lines. Cancer Res 47: 281, 1987

Garewal, H.S., Ahmann, F.R., Schifman, R.B. and **Celniker, A.** ATP Assay: Ability to Distinguish Cytostatic from Cytocidal Anticancer Drug Effects. JNCI 77: 1039, 1986